CLAIMS

What is claimed is:

1. A method of generating and optionally using a responsive cellular profile corresponding to a biological state, the method comprising:

    a) providing a first sample from a first subject, wherein the first subject has a first biological state;

    b) providing a first cell population;

    c) contacting the first sample with the first cell population in vitro;

    d) detecting a plurality of cellular constituents of the first cell population to generate a first responsive cellular profile, wherein the first responsive cellular profile corresponds to the first biological state.

2. A method of claim 1, further comprising:

    e) providing information that describes the first biological state;

    f) creating a database linking the information that describes the first biological state to the first responsive cellular profile.

3. The method of claim 1, further comprising

    e) providing a second sample from the first subject, wherein the first subject has a second biological state;

    f) providing a second cell population;

    g) contacting the second sample with the second cell population in vitro;

    h) detecting a plurality of cellular constituents of the second cell population to generate a second responsive cellular profile, wherein the second responsive response profile corresponds to the second biological state.

4. The method of claim 1, further comprising

    e) providing a second sample from a second subject, wherein the second subject has a second biological state;

    f) providing a second cell population;

    g) contacting the second sample with the second cell population in vitro;

    h) detecting a plurality of cellular constituents of the second cell population to generate a second responsive cellular profile, wherein the second responsive cellular profile corresponds to the second biological state.

5. The method of claim 1, further comprising:

    e) providing *n* additional samples from one or more subjects that may include the first subject, wherein each of the first subject and/or one or more additional subjects has one or more additional biological states;

    f) providing *n* additional cell populations;

    g) contacting each of the *n* additional samples with one of the *n* cell populations in vitro;

    h) detecting a plurality of cellular constituents of each of the *n* cell populations to generate *n* additional responsive cellular profiles, wherein each of the *n* additional responsive cellular profiles corresponds to an additional biological state.

6. The method of claim 3, further comprising comparing the first responsive cellular profile to the second responsive cellular profile, thereby generating a similarity index.

7. The method of claim 3, further comprising comparing two or more responsive cellular profiles and their respective corresponding biological states, thereby generating an inferential set.

8. The method of claim 3, further comprising: providing information that describes the biological state corresponding to one or more of the responsive cellular profiles; and creating a database linking the information that describes each biological state to the corresponding responsive cellular profile.

9. The method of any of claims 1 – 8, wherein each responsive cellular profile is of the same type, and wherein the type is selected from the group consisting of: transcriptional profile, translational profile, protein activity profile and mixed profile.

10. The method of any of claims 1 – 8 wherein each cell population comprises a cell type selected from the group consisting of: blood, fat, endothelial, epithelial, lymph or lymphatic system, skin, liver, muscle, brain, bone, neuronal, kidney, breast, lung, hematopoeitic stem cells and other stem cells, undifferentiated or partially differentiated cell types, any cell type from eukaryotes, prokaryotes, or archae.

11. The method of any of claims 1 - 8 wherein each biological sample is selected from the group consisting of: urine, mucous, tears, blood, saliva, sweat, feces, peritoneal fluid, cerebrospinal fluid, sebum, breast milk, amniotic fluid, lymph, blister fluid, pus, pleural fluid, semen, synovial fluid, a different bodily fluid, tissue secretions, tissue extracts, tissue homogenate, cellular secretions or extracts, an extract of any of the preceding, and a fractionate of any of the preceding.

12. The method of any of claims 1-8 wherein each cell population comprises a panel of multiple, separately obtained cell types, and wherein the cellular constituents of the multiple, separately obtained cell types are measured together.

13. The method of any of claims 1-8 wherein each cell population comprises a panel of multiple, separately obtained cell types, and wherein the cellular constituents of the multiple, separately obtained cell types are measured separately.

14. The method of any of claims 1 - 8 wherein each cell population comprises multiple cell types that have been co-cultured, and wherein the cellular constituents are measured

together.

15. The method of any of claims 1 - 8 wherein each cell population comprises multiple cell types that have been co-cultured, and wherein the cellular constituents are measured separately.

16. The method of any of claims 1 - 8 wherein each of the biological states is associated with either a nuclear or mitochondrial genetic polymorphism or mutation, mitochondrial to nuclear genomic ratio, mitochondrial activity, mitochondrial efficiency, telomere length, average telomere length, telomere length in subsets of cells, the distribution of telomere length, shortest telomere length in individual cells of a cellular type, patterns or states of genomic methylation and other silencing, states of cellular differentiation, or epigenetic genomic modifications.

17. A method of generating and optionally using a responsive cellular profile corresponding to a biological state comprising:

    a) providing a first tissue or cellular sample from a first subject, wherein the first subject has a first biological state;

    b) detecting a plurality of cellular constituents of cells of the first cellular sample to generate a first responsive cellular profile, wherein the first responsive cellular profile corresponds to the first biological state.

18. A method of claim 17, further comprising:

    c) creating a database linking the information that describes the first biological state to the first responsive cellular profile.

19. The method of claim 17, further comprising

    c) providing a second tissue or cellular sample from the first subject, wherein the first subject has a second biological state;

d) detecting a plurality of cellular constituents of cells of the second cellular sample to generate a second responsive cellular profile, wherein the second responsive response profile corresponds to the second biological state.

20. The method of claim 17, further comprising

c) providing a second tissue or cellular sample from a second subject, wherein the second subject has a second biological state;

d) detecting a plurality of cellular constituents of the second cellular sample to generate a second responsive cellular profile, wherein the second responsive cellular profile corresponds to the second biological state.

21. The method of claim 17, further comprising:

c) providing *n* additional tissue or cellular samples from one or more subjects that may include the first subject, wherein each of the first subject and/or one or more additional subjects has one or more additional biological states;

d) detecting a plurality of cellular constituents of each of the *n* tissue or cellular samples to generate *n* additional responsive cellular profiles, wherein each of the *n* additional responsive cellular profiles corresponds to an additional biological state.

22. The method of claim 20, further comprising comparing the first responsive cellular profile to the second responsive cellular profile, thereby generating a similarity index.

23. The method of claim 20, further comprising comparing two or more responsive cellular profiles and their respective corresponding biological states, thereby generating an inferential set.

24. The method of claim 20, further comprising providing information that describes the biological state corresponding to one or more of the responsive cellular profiles; and creating a database linking the information that describes each biological state to the corresponding responsive cellular profile.

25. The method of any of claims 17-24, wherein each responsive cellular profile is of the same type, the type selected from the group consisting of: transcriptional profiles, translational profiles, protein activity profiles and mixed profiles.

26. The method of any of claims 17-24, wherein each cellular sample is selected from the group consisting of: blood, fat, oral cavity, lymph or lymphatic system, skin, liver, muscle, brain, bone, neuronal, kidney, breast, lung, hematopoeitic stem cells and other stem cells, undifferentiated or partially differentiated cell types, other cells types, tissue extracts, cellular secretions or extracts, an extract of any of the preceding, a cellular subtype of any of the preceding, and a fractionate of any of the preceding.

27. The method of any of claims 1-8 or 17-24 wherein the biological state is a state of dietary or nutritional health.

28. The method of claim 27, wherein the state of dietary or nutritional health is selected from the group consisting of: vitamin sufficiency/deficiency, mineral sufficiency/deficiency, other metabolite balance, imbalance, or flux, calorie or caloric restriction, caloric maintenance, caloric overabundance, metabolism, anabolism, catabolism, fuel or energy balance, imbalance, or flux, vegetarianism, a high protein diet, a high fat diet, a high carbohydrate diet, varying ratios of protein, carbohydrates, fat and fiber, varying types of dietary fiber, different amounts and types of protein, fat, carbohydrate, or fiber, the administration of different fuel or energy sources by various means including orally, intravenously, parenterally, enterally, subcutaneously, or topically, varying blood glucose levels, blood glucose kinetics, insulin levels, insulin kinetics, and growth factor levels and kinetics.

29. The method of any of claims 1-8 or 17-24 wherein the biological state is a non-disease state.

30. The method of claim 29 wherein the non-disease state is selected from the group consisting of: normalcy, wellness, healthiness or healthfulness, ion or electrolyte balance,

imbalance, or flux , chronological or biological age, presence or absence and proportion of senescent cells in cells, organs and tissues, presence or absence and proportion of damaged, dying, dead, or apoptotic cells in cells, organs and tissues, hormonal balance, flux or imbalance, or flux, pregnancy, menopause, fatigue, chronic fatigue or unexplained lethargy, difficulty in breathing or other obstructed lung or airway difficulties, acid reflux, difficulty swallowing, difficulty urinating, constipation or difficult bowel movement, thin or cracking skin or other skin dysfunction, blood in urine, blood in stool, unexplained bleeding, pain in the chest, pain in the abdomen, joint pain, pain in the muscles, pain in the neck, pain in the face, jaw pain, eye pain, sinus pain, pain in the head, tinnitus, pain in the head such as caused by headache or migraine headache, unexplained pain, swelling or edema, unexplained swelling or edema, weakness, unexplained loss of balance, dizziness or disorientation, loss of balance, colonization or infection by a microbial pathogen, or blindness or other disability.

31. The method of claim 29 wherein the non-disease state is selected from the group consisting of: psychological, mental, or physical activity, shock, trauma, or stress, or sensitivity, or resistance, recovery from shock, trauma, or to stress, including but not limited to oxidative stress, surgery, radiological exposure, chemical exposure, biological agent exposure, heat or cold stress, exercise, physical strength, speed, or endurance, mental strength, quickness, or endurance, exercise or athletic performance, toxification toxic stress or shock, psychological shock or trauma, physical shock or trauma.

32. The method of any of claims 1-8 or 17-24, wherein the biological state is a pre-disease state.

33. The method of claim 32, wherein the pre-disease state is selected from the group consisting of: pre-diabetes, insulin resistance, glucose intolerance, obstructive lung and other pulmonary difficulties pre-cancer, pre-metastatic cancer, pre-cancer from tobacco use, pre-emphysema, pre-stroke, cardiovascular disease, pre-heart disease, pre-coronary heart disease, pre-liver or kidney disease, dementia, pre-Alzheimer, or apparently

disease-free but aged.

34. The method of any of claims 1-8 or 17-24 wherein the biological state is selected from the group consisting of: allergic reaction, sensitivity to a chemical or biological agent, and or toxification or intoxication with a toxic agent or a drug.

35. The method of any of claims 1 – 8 or 17-24 wherein a therapy, treatment, intervention, or perturbation is used or prescribed to attempt to change the biological state.

36. The method of claim 35, wherein a therapy, treatment, intervention, or perturbation is selected from the group consisting of: dietary change, the administration or application of fuel sources to the patient or subject, exercise, the administration of herbs or dietary supplements, drugs, the administration of natural or synthetic products, lifestyle change, surgery, exercise, physical therapy, acupuncture, chiropractic, addition or subtraction from the subject of biological agents such as living cells, proteins or other metabolites, or genetic constructs.

37. A method of determining the presence, intensity, stage, or level, of a biological state of a subject, the method comprising:

    a) providing a first responsive cellular profile corresponding to the physiological state of the subject;

    b) providing one or more additional responsive cellular profiles corresponding to one or more known related physiological states of the same or different subjects;

    c) comparing the first responsive cellular profile to the one or more additional responsive profiles to identify similar cellular profiles, wherein the physiological state of the subject is similar to the known physiological state that corresponds to the similar cellular profiles.

38. A method of determining the presence, intensity, stage, or level, of a biological state of a subject, the method comprising:

a) providing a plurality of responsive cellular profiles corresponding to a plurality of known related biological states of one or more subjects;

b) analyzing the plurality of responsive cellular profiles corresponding to a plurality of known related biological states to generate an inferential set;

c) providing a responsive cellular profile corresponding to a subject having an unknown physiological state;

d) using the inferential set to predict the biological state of the subject having an unknown biological state.

39. The method of claim 37 or 38, wherein the related biological states are varying degrees of severity of a disease state.

40. The method of claim 37 or 38, wherein the related biological states are varying levels of positive or negative effects of a therapeutic regimen.

41. The method of claim 38, wherein comparing the first responsive cellular profile to the one or more additional responsive profiles comprises determining a measure of correlation between the profiles that are compared.

42. The method of claim 38, wherein the inferential set is generated using a statistical method selected from the group consisting of: a correlative method and a clustering method.

43. The method of claim 38, wherein the inferential set comprises a regression curve and where using the inferential set comprises interpolating or extrapolating to calculate a predictive profile most similar to the responsive cellular profile corresponding to a subject having an unknown physiological state.

44. A method of determining the presence, intensity, stage, or level, of one or more physiological states of a subject, said method comprising:

a) providing an inferential set comprising, for each physiological state, a set of levels

of a plurality of cellular constituents, wherein the variation in the levels of the cellular constituents is predictive of physiological state;

b) providing a responsive cellular profile for the subject;

c) extracting from the inferential set one or a combination of calculated predictive profiles for which similarity is greatest between the responsive cellular profile and the calculated predictive profiles, wherein each calculated predictive profile corresponds to a predicted level of a physiological state of the subject.

45. The method of claim 44 wherein each predicted level of a physiological state of the subject is a level which minimizes the value of an objective function of the difference between the responsive cellular profile and a calculated predictive profile extracted from the inferential set.

46. A method of determining a level of effect of one or more therapies upon a subject, said method comprising:

a) providing an inferential set comprising, for each therapy, a set of levels of a plurality of cellular constituents, wherein the variation in the levels of the cellular constituents is predictive of the level of effect of a therapy;

b) providing a responsive cellular profile for the subject;

c) extracting from the inferential set one or a combination of calculated predictive profiles for which similarity is greatest between the responsive cellular profile and the calculated predictive profiles, wherein each calculated predictive profile corresponds to a predicted level of effect of a therapy on the subject.

47. The method of claim 46 wherein the level of effect of a single therapy is determined.

48. The method of claim 46 wherein the inferential set is correlated to levels of effect of each of the therapies by calibrating the set of levels of a plurality of cellular constituents to one or more defined effects.

49. The method of claim 48 wherein the therapies are adjusted until the responsive cellular profile matches a calculated predictive profile derived from the calibrated inferential set at a desired level of the one or more defined effects.

50. The method of claim 46 wherein one or more of the therapies comprises administration of a pharmacologically or biologically active agent to the subject such as a drug, an antioxidant, a prehormone, a hormone or mixture of hormones, exogenous cell or cells, exogenous tissues, nucleic acids, proteins, or other metabolites, to the subject.

51. The method of claim 46 wherein one or more of the therapies comprise administration of a beverage, a food, a fuel or energy source, or one or more food ingredients to the subject.

52. The method of claim 51, wherein the one or more food ingredients comprises a substance selected from the group consisting of: cellular constituents, fats, proteins, sugars, complex carbohydrates, vitamins, minerals, herbs, herbal supplements, food colorings, food additives and food spices.

53. The method of claim 46 wherein one or more of the therapies comprises administration of a cosmetic or personal care ingredient or formulation, or similar formulation, to the subject.

54. The method of claim 53, wherein the cosmetic or personal care ingredient or formulation is selected from the group consisting of: fats and oils, alcohols, vitamins, preservatives, sugar alcohols such as glycerol, hydroxy acids such as glycolic and lactic acid, emulsifiers such as lecithin, tretinoin, retinol, hydrating agents such as polyethylene glycol, skin creams, soap, sunscreen, deodorant or body-odorant (e.g., perfume or cologne), anti-perspirant, detergent, fabric softener, lotion, hair dye, shampoo, and hair conditioner.

55. The method of claim 46 wherein said subject has a disease state, and the effect of at least one of the one or more therapies reduces or eliminates the symptoms of the disease state

in the subject.

56. The method of claim 46 wherein the effect of at least one of the therapies is an adverse effect.

57. The method of claim 56 wherein the adverse effect is an allergic or toxic effect.

58. The method of claim 46 wherein the predicted level of effect of a therapy is a level which minimizes the value of an objective function of the difference between the responsive cellular profile and a calculated predictive profile extracted from the inferential set for each predicted level of effect of the therapy.

59. The method of claim 45 or 58 wherein the objective function comprises a sum of the squares of differences of the inferential molecular profile and the calculated predictive profile extracted from the inferential set.

60. The method of claim 44 or 46 wherein the subject is a mammal.

61. The method of claim 44 or 46 wherein the subject is a human.

62. The method of claim 44 or 46 wherein the plurality of cellular constituents comprises abundances of a plurality of RNA species present in said cells or cell types, and wherein the responsive cellular profile comprises a transcriptional profile.

63. The method of claim 62 wherein the abundances are measured by a method comprising contacting a microarray with RNA from the cells, or with cDNA derived therefrom.

64. The method of claim 62 wherein the transcriptional profile is generated by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from said cell or cell type treated with biological samples obtained from said subject and (ii) with RNA or with cDNA derived therefrom, from a second cell or cell type treated with biological samples obtained from either (a) said subject from a different time or treated with a different intervention, treatment or therapy, or (b) with RNA or with cDNA derived therefrom, from a second cell or cell type treated with

biological samples obtained from a second subject with or without the same intervention, treatment or therapy.

65. The method of claim 44 wherein the set of levels of a plurality of cellular constituents comprises RNA species known to be increased or decreased in a cell in response to perturbations correlated to the physiological state.

66. The method of claim 46 wherein the set of levels of a plurality of cellular constituents comprises RNA species known to be increased or decreased in a cell in response to perturbations correlated to the level of effect of the therapy.

67. The method of claim 44 or 46 wherein the plurality of cellular constituents comprises abundances of a plurality of protein species present in said cells or cell types, and wherein the responsive cellular profile comprises a translational profile.

68. The method of claim 46 wherein said abundances are measured by a method comprising contacting an antibody array with proteins from said cells, wherein said antibody array comprises a surface with attached antibodies, said antibodies capable of binding with said plurality of protein species.

69. The method of claim 62 wherein said abundances are measured by a method comprising performing two-dimensional electrophoresis of proteins from said cells.

70. The method of claim 44 or 46 wherein the plurality of cellular constituents comprises the activities of a plurality of protein species present in the cell type and wherein the responsive cellular profile comprises an activity profile.

71. The method of any of claims 1 – 8 or 17-24, wherein the biological sample comprises of combined samples, or a pool of samples, from one or more individual subjects.

72. The method of any of claims 1 – 8 or 17 - 24, wherein the information concerning the physiological state of the subject results from a comparison of their responsive cellular profile to another responsive cellular profile obtained by treatment of an cell population

with one or more physical or bioactive agents.

73. The method of claim 72, wherein the one or more physical or bioactive agents are selected from the group consisting of: heat, radiation, drugs, hormones, vitamins, proteins and peptides.

74. The method of any of claims 1 – 8 or 17 - 24, wherein the information concerning the physiological state of the subject results from a comparison of their responsive cellular profile to another responsive cellular profile obtained by co-treatment of a cell population with a biological sample together with one or more biological samples and/or physical and bioactive agents.

75. The method of claim 74, wherein the one or more physical or bioactive agents are selected from the group consisting of: heat, radiation, drugs, hormones, vitamins, proteins and peptides.

76. The method of any of claims 1 – 8 or 17 - 24, further comprising:

a) providing a calibration cell population or cellular sample;

b) contacting the calibration cell population or cellular sample with a calibration agent;

c) detecting a plurality of cellular constituents of the calibration cell population to generate a calibration responsive cellular profile, wherein the calibration responsive cellular profile corresponds to a biological response associated with the calibration agent.

77. The method of claim 76, wherein the calibration agent is a bioactive agent has a predictable effect on a biological pathway or genetic network of interest.

78. The method of claim 76, wherein the calibration agent is selected from the group consisting of: an siRNA, a growth hormone and a drug.

79. The method of claim 76, further comprising comparing one or more responsive cellular profiles with the calibration responsive cellular profile.

80. The method of claim 76, wherein the calibration agent is a cell or cell secretion derived from a cell type selected from the group consisting of: cells from tumors of breast cancer, lung cancer, prostate, colorectal, lymphoma, infected cells, toxified cells.